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Method and device for filling the dosing chamber of an inhaler for the first time

The present invention relates to medicinal inhalers for medical purposes which deliver a given amount of a preferably pharmaceutical fluid over a fairly long period in the form of a "soft" aerosol mist for inhalation ("soft mist™ inhaler" or SMI for short). A device of this kind may be, for example, an inhaler of the Respimat® type, which is described in more detail in WO 97/12687. This type of inhaler is fitted with a cartridge containing a fairly large amount of the active substance formulation. The present invention relates to a further development of the Respimat® system, in which the fitting of the cartridge into the device is improved with a view to speeding up the first use of the spray.

Prior art

The handy inhalers of the Respimat® type or inhalers like the Respimat® Soft® Mist™ Inhaler (SMI), in which a small amount of an aqueous formulation is atomised in amounts of a few microlitres without the use of propellant gases to form an aerosol mist, are one of the latest innovative developments in the field of medical atomisation technology. Because of its cylindrical shape and handy size of less than 9 to 15 cm long and 2 to 4 cm wide this device can be taken anywhere by the patient, so that it is always available for regular daily use in a manner which is convenient to the patient, irrespective of the location.

The basic technical characteristics of these inhalers are disclosed for example in WO 91/14468 or WO 97/12687, particularly in Figures 6a and 6b. In these inhalers, the amount of liquid pharmaceutical formulation to be nebulised by high pressure up to 500 bar is forced through a micronozzle with preferably two nozzle outlets and thereby converted into an aerosol destined for the lungs. Reference is specifically made to the above-mentioned publications, within the scope of the present description.

The Respimat® principle is based on two separate construction units: on the one hand the inhaler which contains all the mechanical components for producing the aerosol, and on the other hand a separate cartridge, which contains the pharmaceutical formulation.

For use the cartridge is pushed onto a cannula formed in the inhaler. Liquid is conveyed through this cannula into a compressing and dosing chamber and from there forced through a micronozzle by the application of pressure.

The cartridge consists of a container filled with the fluid and a closure cap therefor.

Essentially, a Respimat® type nebuliser consists of an upper housing part at the top, a lower housing part which is rotatably mounted relative to the upper housing part and defines the bottom end, a pump housing, the nozzle, a locking clamping mechanism, a spring housing, a spring and the storage container.

The pump housing is in the upper housing part. At the top end of the pump housing is located the nozzle body with the nozzle or the nozzle arrangement. Below this is a compression chamber which may be part of a central tube in the form of a cylindrical bore. Below the compression chamber is the upper end of a cannula in the form of a hollow piston, which projects partially into the central tube and can move axially back and forth therein in a stroke action. The hollow piston is fixedly connected to a power takeoff flange outside the central tube. The power takeoff flange is located on the top end of a spring (helical spring) and is moved thereby. The helical spring is located in a spring housing, which is rotatably mounted on the upper housing part by means of a rotary bearing and can be tensioned and released by means of a locking clamping mechanism. All the components mentioned in this paragraph are located in the upper housing part. The hollow piston extends with its lower, bottom end into the inner space defined by the compression spring. This hollow space is open at the bottom. At the top it may be bounded by the power takeoff flange. The pharmaceutical cartridge is inserted from the bottom end into this cavity in the helical spring and pushed onto the cannula. The lower housing part is then pushed axially over the spring housing. The system comprising the hollow piston, central tube, compression chamber and nozzle constitutes a system for conveying a fluid. The connections between the individual components are sealed off to the outside. The fluid conveying system has only two openings, the lower opening in the hollow piston and the nozzle opening. One opening serves to receive a fluid, while the other, the nozzle opening, serves to deliver said fluid.

The nozzles used are special nozzles, as described for example in WO 94/07607 or WO 99/18530. Reference is made specifically to both these publications.

The nozzle in the nozzle body is preferably microstructured, i.e. produced by micro-engineering. Microstructured nozzle bodies are disclosed for example in WO-94/07607; reference is hereby made to the contents of this specification, especially Figure 1 and the associated description.

The nozzle body consists for example of two sheets of glass and/or silicon securely fixed together, at least one of which has one or more microstructured channels which connect the nozzle inlet end to the nozzle outlet end. At the nozzle outlet end there is at least one round or non-round opening 2 to 10 microns deep and 5 to 15 microns wide, the depth preferably being 4.5 to 6.5 microns and the length being 7 to 9 microns.

If there is a plurality of nozzle openings, preferably two, the directions of spraying of the nozzles in the nozzle body may run parallel to each other or may be inclined relative to one another in the direction of the nozzle opening. In the case of a nozzle body having at least two nozzle openings at the outlet end, the directions of spraying may be inclined relative to one another at an angle of 20 degrees to 180 degrees, preferably at an angle of 60 to 150 degrees, most preferably 80 to 100°.

The nozzle openings are preferably arranged at a spacing of 10 to 200 microns, more preferably at a spacing of 10 to 100 microns, still more preferably 30 to 70 microns. A spacing of 50 microns is most preferred.

The directions of spraying therefore meet in the region of the nozzle openings.

For the nebulisation, the liquid pharmaceutical preparation hits the nozzle body at an entry pressure of up to 600 bar, preferably 200 to 300 bar and is atomised through the nozzle openings into an inhalable aerosol. The preferred particle sizes of the aerosol are up to 20 microns, preferably 3 to 10 microns.

The hollow piston with valve body corresponds to a device disclosed in WO 97/12687. It projects partially into the cylinder of the pump housing and is disposed to be axially movable in the cylinder. The valve body is preferably mounted on the end of the hollow piston which faces the nozzle body.

Reference is made particularly to Figures 1-4 - especially Figure 3 - and the associated passages of description. At the moment of release of the spring the hollow piston with valve body exerts, at its high pressure end, a pressure of 5 to 60 Mpa (about 50 to 600 bar), preferably 10 to 60 Mpa (about 100 to 600 bar) on the fluid, the measured amount of active substance solution. Volumes of 10 to 50 microlitres are preferred, volumes of 10 to 20 microlitres are more preferable, whilst a volume of 10 to 15 microlitres per actuation is particularly preferred.

The locking clamping mechanism contains the spring, preferably a cylindrical helical compression spring, as a store for the mechanical energy. The spring acts on the power take-off flange as a spring member the movement of which is determined by the position of a locking member. The travel of the power take-off flange is precisely limited by an upper stop and a lower stop. The spring is preferably tensioned via a stepping-up gear, e.g. a helical sliding gear, by an external torque which is generated when the upper housing part is turned relative to the spring housing in the lower housing part. In this case, the upper housing part and the power take-off flange contain a single- or multi-speed spline gear.

The locking member with the engaging locking surfaces is arranged in an annular configuration around the power take-off flange. It consists for example of a ring of plastics or metal which is inherently radially elastically deformable. The ring is arranged in a plane perpendicular to the axis of the atomiser. After the locking of the spring, the locking surfaces of the locking member slide into the path of the power take-off flange and prevent the spring from being released. The locking member is actuated by means of a button. The actuating button is connected or coupled to the locking member. In order to actuate the locking clamping mechanism the actuating button is moved parallel to the annular plane, preferably into the atomiser, and the deformable ring is thereby deformed in the annular plane. Details of the construction of the locking clamping mechanism are described in WO 97/20590.

The lower housing part is pushed axially over the spring housing and covers the bearing, the drive for the spindle and the storage container for the fluid.

When the atomiser is operated, the upper part of the housing is rotated relative to the lower part, the lower part taking the spring housing with it. The spring meanwhile is compressed

and biased by means of the helical sliding gear, and the clamping mechanism engages automatically. The angle of rotation is preferably a whole-number fraction of 360 degrees, e.g. 180 degrees. At the same time as the spring is tensioned, the power take-off component in the upper housing part is moved along by a given amount, the hollow piston is pulled back inside the cylinder in the pump housing, as a result of which some of the fluid from the storage container is sucked into the high pressure chamber in front of the nozzle.

The atomising process is initiated by gently pressing the actuating button. The clamping mechanism then opens the way for the power take-off component. The biased spring pushes the piston into the cylinder in the pump housing. The fluid emerges from the nozzle of the atomiser in the form of a spray.

Further details of the construction are disclosed in PCT applications WO 97/12683 and WO 97/20590, to which reference is hereby made.

The storage container (cartridge) is preferably a container having a flange or a closure cap via which the hollow piston of the inhaler can be inserted into the interior. The flange or the closure cap contains a guide passage for the hollow piston with at least one sealing point which prevents air from getting into the container from outside along the hollow piston or fluid from escaping from the container by the same route. The flange or the closure cap may be designed to be releasably or non-releasably connected to the power takeoff flange of the inhaler. Preferably the container is constructed as a collapsible container which is preferably surrounded by a fixed, rigid second container which protects the collapsible first container from damage, *inter alia*. Suitable containers are described in EP 0775076 or WO 99/43571. However, other suitable non-collapsible containers may also be used. The storage container constitutes a self-contained system before it is fitted onto the hollow piston, on which there are no devices to which pressure is to be applied.

Before the first use the still sealed cartridge (the container) has to be pushed onto the cannula of the inhaler. In order to fill the region from the hollow piston to the nozzle with fluid completely for the first time the inhaler known from the prior art has to be tensioned and actuated several times.

Description of the invention

One aim of the present invention is to provide an inhaler of the Respimat® type, which can be operated more quickly than the device known from the prior art after the first insertion of the cartridge.

A further aim of the present invention is to shorten the steps prior to the first operation of an inhaler of the Respimat® type.

A further aim of the present invention is to automate the steps for filling an inhaler of the Respimat® type with fluid for the first time.

Detailed description of the invention

According to the invention the problem is to speed up and automate the process of filling the dead volume in the inhaler. The term dead volume refers to the volume which is created by the interior of the cannula above the fluid level, the inside of the valve, the part of the cylinder above it, including the pressure chamber, and the inner space of the nozzle, minus the part of the volume which is taken up by the region of the hollow piston. In other words, that part of the cannula volume which projects into the fluid after the completion of the insertion process of the cartridge, which is generally at least 90 vol% full, is not taken into account. The system of cannula, cylinder, pressure chamber, nozzle is hereinafter referred to as the fluid conveying system. Thus the dead volume corresponds to the inner volume of the fluid conveying system when the spring is relaxed, minus the proportion filled solely by the principle of the communicating tubes when the cartridge is pushed onto the cannula. The volume which is to be expelled through the atomiser is not included either. This volume is called the fill volume and is generated when the spring of the device is tension and the piston is moved out of the central tube without leaving it. The difference between the two volumes corresponds substantially to the amount of fluid that is to be nebulised (delivery volume).

In detail, the preferred nebuliser may be described as follows. A pump housing is located in a cylindrical upper housing part. A holder for the atomiser nozzle is mounted on its end. The holder contains the nozzle body and optionally one or more filters. The nozzle is located at the upper end of a cylinder tube which is formed in the pump housing. The hollow piston fixed in a power takeoff flange of the locking clamping mechanism. At its end the hollow piston has a valve body. The hollow piston is sealed off to the outside by means of a gasket.

Inside the upper housing part is a first stop on which the power takeoff flange bears when the spring is relaxed. On the power takeoff flange there is a second stop on which the power takeoff flange bears when the spring is relaxed. After the tensioning of the spring a locking member slides between the second stop and a support in the upper housing part. An actuating button is connected to the locking member. The upper housing part ends in a mouthpiece and is closed off by the push-on protective cap.

A cylindrical spring housing with compression spring is rotatably mounted on the upper housing part by means of snap-in lugs and rotary bearing. The cylindrical lower housing part is pushed over the spring housing. Inside the spring housing is the exchangeable storage container for the fluid which is to be atomised. The storage container is sealed off by a stopper through which the hollow plunger projects into the storage container and is immersed at its end in the fluid (supply of active substance solution).

To solve the problem according to the invention it is proposed to relax the excess pressure which has spontaneously formed in the storage vessel (container) or is present therein with the introduction of the storage vessel into the inhaler, with displacement of fluid from the container through the fluid conveying system comprising a hollow piston, cylinder, pressure chamber and nozzle, so that the dead volume of the fluid conveying system is filled with fluid and the nozzle is attached to the fluid supply with the exclusion of air.

According to the invention the excess pressure is supposed to be sufficient to more than completely fill the dead volume with fluid on one side. On the other hand the pressure is only supposed to be high enough for preferably less than 100 microlitres to leave the inhaler through the nozzle as a result of the release of pressure. It is important that at least one and a half times more fluid is forced through the fluid conveying system than corresponds to the dead volume of the fluid conveying system. This compensates any tolerances which may occur as a result of the elasticity of the storage vessel.

In a first embodiment of the invention the excess pressure in the container is generated spontaneously by pushing the container onto the hollow piston of the non-tensioned inhaler. At least that part of the cannula of the inhaler which extends into the container is of a different construction from the embodiment known from the prior art. According to the invention the region of the cannula of the inhaler which extends into the container, should be configured

such that this region displaces at least one and a half times, preferably twice as much fluid as the amount corresponding to the first dead volume. This measure ensures that the pressure which is produced by pushing the storage container onto the cannula inside the container is increased, with the result that the fluid is forced through the cannula towards the nozzle under higher pressure and hence more rapidly as a result of the excess pressure inside the container.

The dead volume of the fluid conveying system of the known system is about 17 microlitres, which is made up of about 10 microlitres of dead volume in the central tube when the spring is not under tension, including the dead space of the pressure chamber, 7 microlitres of dead volume in the capillary (that is the proportion of the capillary volume which is above the fluid level when the totally full cartridge is fitted) and about 100 nanolitres of dead volume of the nozzle. This volume then has to be displaced from the region of the cannula which penetrates into the fluid when the cartridge is fitted onto the cannula. With an outer diameter for the cannula of 1.5 mm and a wall thickness of 1.1 mm, the part of the cannula that is immersed in the fluid has to be about 10.8 mm, in order to displace a volume of 18 microlitres.

However, it has been found that these dimensions do not solve the problem, as the flexible container partially compensates the excess pressure produced.

The problem according to the invention is only completely solved if the displacement volume of that part of the hollow piston that penetrates into the interior of the container is at least 23 microlitres, more preferably at least 34 microlitres.

In order to increase the displacement volume to the preferred levels mentioned above, while keeping the same internal and external diameters for the hollow piston, the length of the hollow piston projecting into the interior of the container must be increased to at least 13.8 mm, preferably to at least 20.4 mm.

In another embodiment the external diameter of the cannula is increased, while keeping the internal diameter and the depth of penetration into the interior of the container the same. In this case an external diameter of at least 1.7 mm, preferably at least 2 mm is useful. This has the advantage that because of the broad effective punching surface of the cannula the initial pressure inside the container is built up more rapidly, so that the pressure on the fluid to escape through the cannula is initially increased more than by extending the piston.

In another embodiment the piston may be extended and at the same time its external diameter is increased. Moreover, only that part of the capillary which dips into the fluid can be shaped accordingly, e.g. have a larger external diameter than the remainder of the cannula.

In every case the length of the hollow piston of 44.2 mm outside the interior of the container should preferably be retained.

In another embodiment the container itself is acted upon by pressure when filled with the pharmaceutical formulation. This may be done for example by filling and sealing the container at low temperatures, e.g. from 4°C to 10°C (cold filling). As it is heated to room temperature the corresponding excess pressure is then generated by the expansion of the fluid.

In yet another embodiment as the container is filled with the pharmaceutical formulation an excess pressure is generated by introducing the pharmaceutical formulation under an excess pressure atmosphere and leaving an air bubble of the corresponding order of magnitude inside the container. Then the container is sealed. In this process the air bubble is compressed during the filling. When the container is pierced with the cannula the air bubble is freed from tension and forces the fluid through the cannula. According to the above remarks the volume difference between the compressed and non-tensioned air bubble is preferably at least 23 microlitres, more preferably at least 34 microlitres. Preferably an air bubble of less than 100 microlitres is left in the container. In this embodiment too the cannula of the inhaler has to dip into the fluid.

Further details of the filling operation can be found in the prior art mentioned above.

As a result of the measures described, an excess pressure of preferably more than 1 mbar, particularly preferably more than 5 mbar, is built up inside the container. The maximum pressure built up should not exceed 50 mbar.

In another embodiment it is not the inhaler but the matching cartridge, i.e. the supply system for the fluid consisting of a container and closure, which is physically changed. A displacement device is formed which when the cartridge is fitted onto the cannula of the inhaler is pushed into the inside of the container and thereby displaces some of the fluid

through the fluid conveying system. Embodiments of this kind are hereinafter illustrated in more detail by means of Figures 1 to 5. The drawings are not to scale and are in the nature of sketches, in some cases.

A typical cartridge is described for example by Fig. 1. The closure (1) comprises a device (2) in the form of a connector. The connector can optionally displace some of the contents of the container (3) during the closing process. The immersion connector (2) for its part comprises a passage or guide (12) for the cannula (18) of the inhaler. The connector (2) is initially sealed at the bottom. The immersion connector (2) displaces fluid from the container when the closure cap is put on and thereby ensures that after sealing the container is at least 90, preferably 95 % full by volume. The closure cap also has an encircling bead (4) on the inside (crimp edge) which engages underneath a cylindrical ring (5) running round the outside of the neck of the container, at the lower edge of the closure cap (1) in the closure position. While the closure cap (1) is pushed on the edge of the closure cap is expanded and the bead (4) abuts on the ring (5) to form a seal, so that the inside (7) of the cap only communicates with the outside through one or more vent openings (6). The vent opening(s) is (are) arranged for example in the outer part of the ring (5). In the closure position the gap between the flat part of the closure cap (1) and the upper edge of the neck of the container, which is optionally provided with an encircling rib (8) to improve the seal, is filled by a gasket (9) and in this way the interior of the container (3) is reliably sealed off from the interior (7) of the cap, which surrounds the sealing ring (9) and the neck of the container (3). The internal diameter of the sealing ring (9) is expediently chosen so as to fit tightly against the device (2). The vent opening(s) (6) may also be located elsewhere on the exterior of the cap, e.g. laterally in the cylindrical part of the cap. The immersion connector has a pierceable base (10).

In a preferred embodiment the container (3) consists of a dimensionally stable outer container and a readily deformable inner bag (3b) which collapses when fluid is removed. Containers of this kind are described for example in European Patent 532 873, the contents of which are hereby incorporated by reference. The device (11) serves to attach the deformable inner bag (3b) to the inner wall of the outer rigid container (3a) facing the bag (3b).

Figure 2 shows a preferred embodiment of the closure cap according to the invention, wherein the inner chamber of the connector has a special guide (12) for a cannula for removing fluid. In the present instance, the vent openings (6) are provided on the upper part of the container (3). The vent openings may alternatively also be provided on the closure cap. If desired the guide (12) may be constructed as a press fit for the cannula (18) or an O-ring seal (13) may be mounted therein.

Figure 3a shows an embodiment of the invention wherein underneath the guide (12) a cavity is formed in the immersion connector (2), in which there is a displacement member (14) in the form of, for example, a stopper, cylinder, cork, etc., which is pushed at least partly into the container (3) when the cannula is passed through the guide (12) and thereby helps to build up the desired excess pressure inside the container. A displacement member of this kind may be located at any point in the guide (12). The shape of the displacement member is preferably cylindrical. The displacement member preferably consists of a plastic such as polyethylene, polypropylene, etc. On its side directed towards the top end of the closure the displacement member may have a recess in which the cannula can engage.

Preferably the displacement member is constructed as a punch which can only partially emerge from the guide (12). In this case at least part of the wall of the displacement member (14) and the wall of the guide (12) may interact to form a fluidtight seal. In order that the displacement member (14) cannot leave the guide (12), stop means in the form of an encircling edge, for example, may be formed at the upper end of the displacement member (14), which interact with stop means - e.g. again in the form of an encircling edge - at the lower end of the guide (12). This prevents fluid from flowing into the space which was previously filled by the displacement member (14), so that no pressure compensation can take place in this way. Alternatively, guide channels may be formed on the displacement member (14), which interact with complementary means on the guide, the guide channels no longer being formed at the top of the displacement member (14). Other stop means for a system of this kind are described inter alia under Figure 4 or in the prior art.

In a preferred embodiment the displacement member may have a bore (19) (Fig. 3b), in which the cannula engages by the force of friction. This prevents the displacement member from dropping into the container after leaving the guide (12). Preferably, the bore may have a press fit or constriction (21) in which the cannula engages. The bore is shaped such that the cannula (18) is in contact with the fluid in the container. For this purpose the bore may constitute a linear passage.

In a variant of this embodiment the bore for receiving the cannula by frictional engagement is not a through-bore and is constructed so that the capillary can only be partially pushed into the bore. As a result a cavity (20) is formed underneath the capillary. For this purpose a constriction (21) may be formed in the bore, for example, preventing the capillary from being

pressed forward any more. The displacement member then has further capillaries (22) which lead from the exterior of the displacement member to the cavity. If these additional capillaries of the displacement member are in the form of microcapillaries, fluid is constantly transported from outside into the cavity, thus ensuring that the cannula of the inhaler is always supplied with fluid even during the emptying of the container. An embodiment along these lines is shown, not to scale, in Figures 3c and 3d.

Preferably the displacement member in this variant is constructed as an integral, capillaried, open-pored, porous storage medium for fluid. In other words the displacement member simultaneously acts as a sponge conveying fluid into its interior. The displacement member may be a dimensionally stable body with a fluid-pervious wall, filled with sintered or non-sintered powder, or a woven or knitted or non-woven structure or a wad of fibres. It may consist of plastics, ceramics, glass, metal or a natural material.

Figures 4a and 4b show another embodiment in which the immersion connector is composed of at least two sleeves (15, 15', 15'') fitting telescopically one inside the other. The inner sleeves in each case have stop means (16) at their upper end, which cooperate with corresponding inwardly directed stop means at the lower end (17) of the outer sleeve and thus ensure that an inner sleeve cannot be pushed right through an outer sleeve. The stop means are preferably edges. Preferably, the individual cylinder-like sleeves fit together to form a seal. The bottom of the innermost sleeve is sealed to begin with, so that, when the container is pushed on, the cannula (18) pushes apart the sleeves which are still nesting in one another before it pierces the base (22) (Figure 4b). In this way the immersion connector is extended while the container is being pushed onto the cannula (18), and thus itself acts as a displacement member which builds up an excess pressure in the fluid-filled interior of the container.

The internal diameter of the innermost sleeve may be constructed as a press fit for the sleeve, or an O-shaped gasket is provided here, for example, to seal the cannula (18) off to the outside.

In the equivalent embodiment according to Figures 5a and 5b the lower region of the immersion connector (19) is pleated in the manner of an accordion (bellows) (Figure 5a). The guide (12) extends from the top part of the closure cap to the pleated end of the immersion

connector. The bottom part of the immersion connector is constructed, as in all the embodiments, so that it can be pierced by the cannula. In this embodiment more force is needed to pierce the bottom part than to pull apart the bellows region. If the cannula (18) is passed through the guide (12), the pleated region is opened out before the bottom part is pierced, so that once again the enlarged immersion connector acts as a displacement member which creates excess pressure inside the container (Figure 5b). As the excess pressure is only slight there is little danger of the excess pressure being compensated by the compression of the extended bellows instead of by the displacement of the fluid through the fluid conveying system. This danger can additionally be countered by a suitable choice of material.

In the alternative embodiments in Figures 4 and 5 the pressure needed for piercing is controlled, for example, by means of the thickness of the bottom part.

Further details of the basic structure of the closure cap or the container can be found in EP 0775076.

These latter embodiments of the invention described above may be constructed analogously to a closure system according to EP 1058657 in the form of a flange provided on a container.